

REMARKS

In the Claims:

Claims 22-26 are currently pending.

Applicants respectfully request that the Examiner enter the Response and Request for Reconsideration filed December 30, 2005 in connection with the above-identified case and consider the following additional remarks, which respond to both the final Office action mailed 1 November 2005 and the Advisory action mailed 22 February 2006.

Rejections:

35 U.S.C. § 101

Claims 22-26 stand rejected under 35 U.S.C. § 101 as allegedly not being supported by either a credible, specific and substantial utility or a well established utility. In particular, the Office and Advisory actions allege that “the results of the MLR assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLC assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary.” (Page 6 of the Office action mailed 1 November 2005 and Continuation Sheet of the Advisory action mailed 22 February 2006). In addition, the Office and Advisory actions allege that “[t]he specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation . . . and the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion.” (Page 6 of the Office action mailed November 1, 2005 and Continuation Sheet of the Advisory action mailed 22 February 2006).

Applicants respectfully disagree. As previously argued, Applicants maintain that the claimed antibodies, which bind the PRO 361 polypeptide, find utility in preventing

suppression of an immune response, as asserted at Example 34, found on page 141 of the present specification.

In rejecting Applicants' assertion of utility based on Applicants' reliance on the MLR assay, the Office applies an incorrect legal standard. When the proper legal standard is applied, it is clear that the results obtained with PRO361 in the MLR assay provide a specific and substantial utility for the claimed antibodies that bind the PRO361 polypeptide.

In interpreting the utility requirement set forth in 35 U.S.C. § 101, the CCPA, in *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ (BNA) 881 (C.C.P.A. 1980), acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, *even though they may not establish a specific therapeutic use*. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility." *Id.* at 856, 206 USPQ (BNA) at 883.

In *Cross v. Iizuka*, 753 F.2d 1047, 224 USPQ (BNA) 739 (Fed. Cir. 1985), the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between." *Id.* at 1050, 224 USPQ (BNA) at 747. The court perceived "no insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility." *Id.*

The case law has also clearly established that applicants' statements of utility will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380,1391, 183 USPQ (BNA) 288, 297 (C.C.P.A. 1974). *See also In re Jolles*, 628 F.2d 1322, 206 USPQ (BNA) 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ (BNA) 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ (BNA) 209, 212-13 (C.C.P.A. 1977). Compliance with 35 U.S.C. §101 is a question of fact.

Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d (BNA) 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

In the present case, rejection of claims 22-26 for alleged lack of utility is improper because the Office has failed to make a *prima facie* showing of lack of utility. Indeed, although the Office action provides an explanation of the MLR assay as that assay typically is used, the reasoning for rejecting Applicants' reliance on the MLR assay provided in the Office action does not alone make it more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' statement of utility. Making a *prima facie* showing that one of ordinary skill in the art would doubt the truth of Applicants' statement of utility is a significant burden to overcome because statistical certainty regarding Applicants' assertion of utility is not required to satisfy 35 U.S.C. § 101. *Nelson v. Bowler*, 626 F.2d at 856-857, 205 USPQ at 883-884. Indeed, where, as here, an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed as "wrong" even where there may be some reason to question the assertion. MPEP § 2107.02.

Furthermore, in at least two related cases, U.S. Patent Application Serial Nos. 09/944,929 and 10/677,471, the Office has acknowledged that, in view of US Patent No. 5,817,306, "the MLR assay is art recognized for identifying molecules which suppress an immune response." See Page 6 of the Examiner's Answer (Tabs A and B). Applicants note that in addition to US Patent No. 5,817,306, which is relied on by the Office in the two above-identified related cases, other patent literature, including US Patent No. 5,648,376 at col. 11, ll 24-27; US Patent No. 5,801,193 at col. 8, ll. 6-15; US Patent No. 6,472,518 at col. 20, ll 21-25, and US Patent No. 6,743,014 at col. 21, ll 16-18 recognize the MLR assay as an *in vitro* predictor of *in vivo* immunosuppressant activity. Applicants note that this

patent literature is consistent with the other non-patent literature that Applicants previously made of record, including the references submitted with the Amendment and Request for Reconsideration mailed August 3, 2005, and the following references submitted with the Response and Request for Reconsideration mailed 27 December 2005: Wolos *et al.*, "Immunomodulation by an inhibitor of S-adenosyl-L-homocysteine hydrolase: inhibition of *in vitro* and *in vivo* allogeneic responses." *Cell Immunol.* 1993 149(2):402-8; Fung-Leung *et al.*, "Tepoxalin, a novel immunomodulatory compound, synergizes with CsA in suppression of graft-versus-host reaction and allogeneic skin graft rejection." *Transplantation.* 1995 60(4):362-8; Townsend *et al.*, "Combination therapy with a CD4-CDR3 peptide analog and cyclosporine A to prevent graft-vs-host disease in a MHC-haploidentical bone marrow transplant model." *Clin Immunol. Immunopathol.* 1998 86(1):115-9; Townsend *et al.*, "Inhibitory effect of a CD4-CDR3 peptide analog on graft-versus-host disease across a major histocompatibility complex-haploidentical barrier." *Blood.* 1996 88(8):3038-47; Furukawa *et al.*, "Immunomodulation by an adenylate cyclase activator, NKH477, in vivo and vitro." *Clin Immunol. Immunopathol.* 1996 79(1):25-35. Thus, Applicants respectfully submit that the asserted utility based on the MLR assay is a credible, specific, and substantial utility and therefore satisfies the utility requirement of 35 U.S.C. § 101.

Moreover, the specification discloses sufficient information about the controls used with the MLR assay. For example, page 3.12.7 of *Current Protocols in Immunology*, which is incorporated into the specification by reference, states:

Separate wells with control cultures should be set up that include – for each dose of responder and stimulator cells – replicate wells of responder cells with irradiated or mitomycin C-treated syngeneic stimulator cells. Values obtained from these controls reflect "background" proliferation values (see step 9 of the basic protocol). Other negative controls often included are wells with stimulator cells alone and wells with responder cells alone. These are not used for the calculation of the data, but are useful to compare with background proliferation values; the latter should not be much higher (<2-fold) than those obtained with stimulator or responder cells alone. Higher background values indicate potential autoreactivity.

At page 141 of the specification, Applicants disclose that the procedure followed in carrying out the MLR assay of Example 34 is forth in *Current Protocols in Immunology*. Therefore, one of ordinary skill in the art would understand that the controls discussed above were used in carrying out the MLR assay with the PRO361 polypeptide. Further, the specification discloses that additional controls including either 100 microliters of cell culture media or 100 microliters of CD4-IgG were used. The Office and Advisory actions allege that it is not clear how CD4-IgG would control for background stimulation or provide for a measure of maximal stimulation. However, Applicants respectfully maintain that one of ordinary skill in the art would appreciate that CD4-IgG is an antibody that might be used as a negative control by blocking or preventing activation of allogeneic responder cells. Additionally, skilled artisans would appreciate that cell culture media would serve as a control by providing a measure of background levels. As quoted above from *Current Protocols*, other useful controls are those that can be used for comparison with background proliferation values (e.g., culture media and CD4-IgG). Controls such as those used in the MLR assay described in the specification help ensure that statistically significant results are obtained.

Significantly, the controls disclosed in *Current Protocols* and used by Applicants are art recognized as sufficient controls for use in the MLR assay. For example, in the MLR assay described in U.S. Patent No. 5,648,376, several controls similar to those described in the *Current Protocols in Immunology* reference were used, including addition of irradiated responder cells to responder cells with or without the test compound and evaluation of wells containing either only irradiated responder or only stimulator cells. See e.g., col. 17, ll. 52-57 of US Patent No. 5,648,376. Further, Applicants respectfully submit that the discussion of controls presented in the present specification is sufficient given the level of skill and knowledge in the art of the MLR assay. For example, there are several patent references discussing the MLR assay, and relying on the results of that assay for utility support, that do not provide any detail regarding what, if any controls were used, or how such controls were used. See e.g., US Patent No. 5,801,193, cols. 8-9; US Patent No. 6,734,014, col. 34, ll. 45-56; and US Patent No. 4,950,647, cols. 6-8.

In addition to explaining how to conduct the MLR assay, Example 34 of the present specification, through reference to the *Current Protocols in Immunology*, also explains how to calculate the results obtained from the MLR assay. Specifically, the data is computed as the difference in cpm of stimulated (experimental) and control (no test substance added) cultures. This is done by subtracting the arithmetic mean of cpm from triplicate control cultures from the arithmetic mean of cpm from corresponding test cultures. Alternatively, the data may be calculated as the ratio of cpm of test and control cultures. This is done by dividing the arithmetic mean of cpm from stimulated cultures by the arithmetic mean of cpm from control cultures. Thus, Applicants have provided sufficient detail in the specification, either explicitly or through incorporation by reference, about the MLR assay, how the assay is performed, what controls are used and how they are used, and how the data is calculated.

According to the specification, “[a]ny decreases below control is considered to be a positive result for an inhibitory compound, with decreases of less than or equal to 80% being preferred.” This standard is art recognized for identifying compounds with immunosuppressive characteristics. For example, in his declaration, Dr. Sherman Fong, Ph.D. explains that it is his scientific opinion that “a PRO polypeptide shown to inhibit T-cell proliferation in the MLR assay where the activity is observed as 80% or less of the control, as specified in the present application, would be expected to find practical utility when an inhibition of the immune response is desired, such as in autoimmune diseases.” (Page 3, paragraph 10 of the Fong Declaration (previously submitted)). Significantly, according to the Manual of Patent Examining Procedure (the “MPEP”), Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement.

Furthermore, the Federal Court of Appeals held in *In re Alton*, “We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner.” *In re Alton, supra*. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines, Part IIB, 66 Fed. Reg. 1098 (2001), which state, “Office

personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Fong Declaration) states that "it is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay where the activity is observed as 80% or less of the control, as specified in the present application, would be expected to find practical utility when an inhibition of the immune response is desired, such as in autoimmune diseases." Therefore, barring evidence to the contrary regarding the above statement in the Fong Declaration, this rejection is improper under both the case law and the Utility guidelines.

Moreover, the patent literature provides further support that Dr. Fong's opinion is an art accepted standard for identifying compounds with immune inhibitory activity. For example, at col. 6, ll 16-19, U.S. Patent No. 5,958,403 states that "[u]seful constructs are also those which provide a mixed lymphocyte reaction (MLR) by decreasing proliferation by 20%, more preferably 40%, and most preferably by 60% relative to control cells."

The specification clearly states that PRO361 tested positive in the MLR assay. Therefore, although no explicit data is provided, in light of the significant details provided about the MLR assay, how it was performed, what controls were used, how they were used, and how the positive result was determined, one of ordinary skill in the art can conclude that PRO361 exhibited a level of inhibition greater than any inhibition seen with the controls and can conclude that PRO361 has immunosuppressant characteristics. Thus, as asserted in the specification, the claimed antibodies have utility in preventing immunosuppression. This is sufficient to satisfy the utility requirement. As stated in *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ (BNA) 881 (C.C.P.A. 1980), tests evidencing pharmacological activity of a compound establish practical utility, even though they may not establish a specific therapeutic use.

Thus, although the specification may not provide actual data values for levels of immunosuppression achieved using the PRO361 polypeptide in the MLR assay, the

specification does provide ample description of the MLR assay, including description of the controls used in the assay, and ample description of how to evaluate results obtained from the MLR assay data. Indeed, in view of these significant teachings and the high level of skill and understanding in the art, the lack of explicit data does not make it more likely than not that one of ordinary skill in the art would doubt Applicants' assertion of utility for the PRO361 polypeptide. Therefore, Applicants respectfully submit that claims 22-26 are supported by a specific, substantial and credible utility and respectfully request that this ground of rejection be withdrawn.

35 U.S.C. § 112, first paragraph

Enablement

The Examiner contends that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants respectfully disagree. As discussed above, the claimed antibody has the specific, substantial, and credible utility binding to a polypeptide that inhibits the proliferation of stimulated T-lymphocytes as demonstrated in the MLR assay experiment discussed in Example 34 at page 141 of the application. Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 22-26 under 35 U.S.C. § 112 ¶1 for alleged inadequate disclosure on how to use the claimed invention.

US App Ser No **10/735,014**

Response to the Office action mailed **1 Nov 2005** and to the Advisory action mailed **22 Feb 2006**

Request for Continued Examination mailed **22 March 2006**

SUMMARY

Applicants believe that currently pending Claims 22-26 are patentable and respectfully request allowance thereof. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite prosecution of this case.

Respectfully submitted,



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/944,929	08/31/2001	Kevin P. Baker	P2548PIC21	2450
7590 01/05/2006 BRINKS, HOFER, GILSON & LIONE PO BOX 10395 Chicago, IL 60611-5599			EXAMINER VOGEL, NANCY S	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 01/05/2006

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/944,929
Filing Date: August 31, 2001
Appellant(s): BAKER ET AL.

C. Noel Kaman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 02 September 2005 appealing from the
Office action mailed 06 October 2004.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

The claims are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The claims are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

It was previously asserted by the Examiner that insufficient evidence was provided to support the position that the MLR assay was an art recognized *in vitro* assay that was predictive of general immune responses *in vivo*. Several references were cited during the prosecution of the instant application which demonstrated either a showing that the results of the MLR assay were consistent with *in vivo* activity or were inconsistent with *in vivo* activity. Upon review of the prior art, the Examiner found a patent that states "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules *in vitro* that are useful for treating graft versus host disease. The results obtained from these assays are generally predictive of their *in vivo* effectiveness." (See column 12, lines 36-

Art Unit: 1636

41 of US Patent No. 5,817,306). Therefore, it is conceded that the MLR assay is art recognized for identifying molecules which suppress an immune response.

However, another basis for rejecting the claims for lack of utility has been the lack of support in the specification for the assertion that the polypeptide encoded by the DNA of the instant claims actually acts as an inhibitor of the proliferation of stimulated T-cells. In Example 34 on page 141, it is stated that "Any decreases [sic] below control is considered to be a positive result for an inhibitory compound, with decreases of less than or equal to 80% being preferred. However, any value less than control indicates an inhibitory effect for the test protein." (lines 33-35). The specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay. The specification provides no information at all regarding the results of the assay except that a certain protein tested positive and the statement that **"any value less than control indicates an inhibitory effect for the test protein"**.

If the claimed invention is to be used for therapeutic inhibition of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? The previous Office actions go into great depth regarding the nature of the MLR assay and host those skilled in the art use this assay and what kind of determinations can be made about compounds which are tested in this assay. The MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,471	10/02/2003	Kevin P. Baker	10466/484	1021

7590 01/05/2006

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ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 01/05/2006

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/677,471
Filing Date: October 02, 2003
Appellant(s): BAKER ET AL.

C. Noel Kaman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/2/05 appealing from the Office action
mailed 11/2/04.

- US Patent No. 5,817,306 HASKILL et al. 10-1998 (newly cited by Examiner)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

The claims are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The claims are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

It was previously asserted by the Examiner that insufficient evidence was provided to support the position that the MLR assay was an art recognized *in vitro* assay that was predictive of general immune responses *in vivo*. Several references were cited during the prosecution of the instant application which demonstrated either a showing that the results of the MLR assay were consistent with *in vivo* activity or were inconsistent with *in vivo* activity. Upon review of the prior art, the Examiner found a patent that states "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules *in vitro* that are useful for treating graft versus host disease. The results obtained from these

assays are generally predictive of their *in vivo* effectiveness." (See column 12, lines 36-41 of US Patent No. 5,817,306). Therefore, it is conceded that the MLR assay is art recognized for identifying molecules which suppress an immune response.

However, another basis for rejecting the claims for lack of utility has been the lack of support in the specification for the assertion that the polypeptide of the instant claims actually acts as an inhibitor of the proliferation of stimulated T-cells. In Example 34 on page 141, it is stated that "Any decreases [sic] below control is considered to be a positive result for an inhibitory compound, with decreases of less than or equal to 80% being preferred. However, any value less than control indicates an inhibitory effect for the test protein." (lines 33-35). The specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay. The specification provides no information at all regarding the results of the assay except that a certain protein tested positive and the statement that **"any value less than control indicates an inhibitory effect for the test protein"**.

If the claimed invention is to be used for therapeutic inhibition of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? The previous Office actions go into great depth regarding the nature of the MLR assay and how those skilled in the art use this assay and what kind of determinations can be made about compounds which are tested in this assay. The MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual. This reactivity is governed by the antigenic